Re-irradiation in the thorax – An analysis of efficacy and safety based on accumulated EQD2 doses

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Abstract: Introduction: Thoracic re-irradiation remains a challenge regarding the balance of local efficacy and acceptable toxicities. In this retrospective analysis we analyzed dosimetrical and clinical data of patients treated with thoracic re-irradiation based on accumulated EQD2Gy doses. Methods and material: We retrospectively analyzed the data of 42 consecutive single-institutional patients treated with repeated courses of thoracic radiotherapy from 12/2011 to 01/2017. Accumulated EQD2 dose distributions were calculated and dose parameters for organs at risk and target volumes were analysed. Results: The median prescription dose was 42.2 Gy (10–70.6 Gy) for all RT courses. The median Dmean of both lungs was 10.1 Gy3 (range: 1.9 Gy3–17.9 Gy3) with a maximum D0.1 cc of 253.86 Gy3. The median D0.1 cc of the esophagus was 62.2 Gy3 with a maximum of 103.78 Gy3. The maximum D0.1 cc for the bronchial tree was 187.33 Gy3 (median 74.35 Gy3) and for the Aorta 216.1 Gy3 (median 70.9 Gy3). Median OS after first re-irradiation was 19 months (range 1–45 months). 12-month local control after a course of re-irradiation was 52.6%. 80% of patients suffered from a G1–G2 toxicity, most frequently coughing. One patient suffered from a G5 complication probably unrelated to re-irradiation. Conclusion: Even though several organs at risk received maximum accumulated doses of >100 Gy3, thoracic reirradiation resulted in an acceptable toxicity profile. Local tumor control and overall survival remained encouraging even after multiple courses of thoracic radiotherapy.

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Original Article

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ABSTRACT

Introduction: Thoracic re-irradiation remains a challenge regarding the balance of local efficacy and acceptable toxicities. In this retrospective analysis we analyzed dosimetrical and clinical data of patients treated with thoracic re-irradiation based on accumulated EQD2Gy doses.

Methods and material: We retrospectively analyzed the data of 42 consecutive single-institutional patients treated with repeated courses of thoracic radiotherapy from 12/2011 to 01/2017. Accumulated EQD2 dose distributions were calculated and dose parameters for organs at risk and target volumes were analysed.

Results: The median prescription dose was 42.2 Gy (10–70.6 Gy) for all RT courses. The median Dmean of both lungs was 10.1 Gy_3 (range: 1.9 Gy_3–17.9 Gy_3) with a maximum D0.1 cc of 253.86 Gy_3. The median D0.1 cc of the esophagus was 62.2 Gy_3 with a maximum of 103.78 Gy_3. The maximum D0.1 cc for the bronchial tree was 187.33 Gy_3 (median 74.35 Gy_3) and for the Aorta 216.1 Gy_3 (median 70.9 Gy_3). Median OS after first re-irradiation was 19 months (range 1–45 months). 12-month local control after a course of re-irradiation was 52.6%. 80% of patients suffered from a G1–G2 toxicity, most frequently coughing. One patient suffered from a G5 complication probably unrelated to re-irradiation.

Conclusion: Even though several organs at risk received maximum accumulated doses of >100 Gy_3, thoracic reirradiation resulted in an acceptable toxicity profile. Local tumor control and overall survival remained encouraging even after multiple courses of thoracic radiotherapy.

Thoracic re-irradiation for primary or metastatic intrathoracic lesions remains a challenge regarding the balance of a locally effective treatment and acceptable treatment related toxicities. Patients with primary lung tumors have a high risk of locoregional recurrence, a second primary lung cancer or thoracic metastases [1–3]. Besides patients with primary lung cancer, also patients with other primary tumors might require repeated treatment for intrathoracic metastases [4–7].

In the past, re-irradiation was often limited to a palliative treatment dose. With the introduction of intensity-modulated and image-guided radiotherapy as well as stereotactic body radiotherapy (SBRT), conformal and more precise treatment has become possible with the ability to deliver locally ablative radiation doses with acceptable treatment related toxicities [6,8–10]. This also applies to re-irradiation, e.g. in patients with locoregionally recurrent primary tumor or patients in an oligometastatic setting for whom a curative treatment intend may still apply. Another group of patients may benefit from palliative re-irradiation to ease tumor related symptoms like pain or dyspnea [11–16].

Several mostly retrospective analyses of thoracic re-irradiation that published in the recent years. Most studies described the re-irradiation plans only separately and independently from each other; few studies calculated accumulated dose distributions of the physical dose distributions to better describe the radiation doses administered both to the target volume and the organs at risk. Especially regarding SBRT the results are promising with a good efficacy and acceptable toxicity [6–10,17,18].

Although these data are encouraging the true tolerance of organs at risk is largely unknown and the decision of re-irradiation is mostly based on personal experience. The goal of this analysis was to estimate the tolerance of thoracic organs-at-risk (OAR) to re-irradiation by calculating accumulated dose distributions using deformable image registration and dose conversion to 2 Gy biologically equivalent doses (EQD2).

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Methods and materials

Patient characteristics

We retrospectively analyzed the data of 42 patients that received repeated high-dose thoracic radiotherapy from December 2011 to January 2017. Repeated high-dose radiotherapy was defined as: (a) at least two courses of thoracic radiotherapy, (b) at least one course consisting of a radical radiotherapy regimen of at least 50 Gy in 2 Gy equivalent, (c) overlap of at least the 50% isodose levels from 2 courses. The local ethics committee approved this retrospective analysis (BASEC-Nr: 2017-01027). Most patients had non-small cell lung cancer (NSCLC, n = 20), followed by esophageal cancer (n = 6) and small-cell lung cancer (SCLC, n = 4). All patients were discussed in a multidisciplinary tumor board prior to treatment. Independent of the thoracic radiotherapy, patients also received additional radiotherapy to other anatomical sites, e.g. analgetic radiotherapy for painful bone metastases. During the initial treatment course before re-irradiation, 69% of patients received systemic therapy, most of which received chemotherapy (85.7% of patients receiving systemic therapy) followed by the combined treatment with chemotherapy and immunotherapy (7.1%). Following first re-irradiation, 52.4% of patients received systemic therapy, again mostly chemotherapy (68.2% of patients receiving systemic therapy) followed by immunotherapy (22.7%). Further patient characteristics are shown in Table 1.

Table 1
Patient characteristics.

	n	%
Gender		
male	11	26.2
female	31	73.8
Primary tumor		
NSCLC	21	50.2
SCLC	4	9.5
esophageal carcinoma	6	14.3
pleural mesothelioma	3	7.1
Metastases of extrathoracic primary tumor	4	9.5
other	4	9.5
Initial UICC stage		
1	9	21.4
2	5	11.9
3	11	26.2
4	15	35.7
unknown	2	4.8
ECOG at 1st Re-irradiation		
0–1	37	88.1
2–3	5	11.9
ECOG at further re-irradiation		
0–1	9	21.4
2–3	1	2.4
Systemic theapies before first re-irradiation		
None	13	31.0
Chemotherapy	24	57.1
Targeted Therapy	1	2.4
Immunotherapy	1	2.4
combination	2	4.8
Systemic theapies after first re-irradiation		
None	20	47.6
Chemotherapy	15	35.7
Targeted Therapy	1	2.4
Immunotherapy	5	11.9
combination	0	0.0
unknown	1	2.4
Age at first re-RT (years)		
median	69.5 years	
range	35–92 years	

Radiation treatment planning and delivery

Planning CT was acquired as 3D or 4D-CT with retrospective amplitude-based image sorting. If necessary, an additional 3D-CT was performed in free breathing to allow for contrast i.v. injection. Gross tumor volume (GTV) was contoured as the visible tumor in the planning CT supplemented by information from i.v. contrast 3D-CT or further imaging including FDG-PET or magnetic resonance imaging (MRI) if available. For non-SBRT treatments, an additional clinical target volume (CTV) was generated with a 5 mm margin around the GTV. An additional margin was added to create the planning target volume (PTV). For SBRT, the internal target volume (ITV) was generated as a composite GTV from the different amplitude-based reconstructed CT scans complemented by a margin of 5 mm to derive the planning target volume (PTV); no separate CTV was generated for SBRT.

All plans were calculated by a radiation therapy technologist using institutional constraints for the organs at risk and target prescription standards. For the first radiation treatment, institutional constraints for thoracic irradiation were based on published recommendations (QUANTEC) [19–21]. For re-irradiation, there was a case-by-case decision on cumulative allowance (Spinal cord: according to Nieder et al. [22]; esophagus and bronchial tree according to published reports on NSCLC dose escalation or SBRT protocols; cum. EQD2Gy D0.1 cc <100 Gy, if no relevant PTV compromise necessary). All plans were reviewed and consented by at least 2 board certified senior radiation oncologists.

For treatment planning, Eclipse software™ (Varian medical systems) was used. If necessary immobilization by individualized vacuum cast or abdominal compression was used.

EQD2 sum plans and statistical analysis

EQD2 sum plans were calculated for all courses of thoracic radiotherapy using the software solutions Eclipse (Version 15.6.04, ARIA ® OIS for Radiation Oncology, Varian Medical Systems) and MIM Vista (Version 6.7.9, MIM Software Inc. VR, Cleveland, OH). First the CT Scans, dose distribution and the structure sets of all relevant courses were exported from ARIA to MIM. After inserting the number of fractions, the structures were matched with the different α/β-values. To calculate the EQD2 the following formula was used:

$$EQD2 = D \times \{d + (\alpha/\beta)\}/\{2Gy + (\alpha/\beta)\}$$

The α/β-values for the target volume were 10, for the myelon 2 and for the body and the other organs at risk 3. Thereafter MIM converted the physical dose distributions to EQD2 dose distributions based on the LQ model above. EQD2 dose distributions were transferred back to Aria where accumulated dose distributions were calculated. As a first step, image registration was performed using rigid automatic bone match (translation and rotations). This was followed by non-rigid image registration. Accumulated dose distributions were calculated on the latest CT scan and the corresponding EQD2 plans and plan sums were generated. Dose volume parameters were calculated for all relevant organs at risk and target volumes.

Endpoints and toxicity definitions

During treatment, all patients were monitored weekly for acute treatment related toxicity. Follow-up 6 weeks after completion of RT and every 3–4 months thereafter included physical examination and CT, PET-CT or MRI scans where appropriate according to the physicians discretion until tumor progression. Toxicity was scored according to the National Cancer Institute CTCAE v4.0 criteria. Toxicity was defined as either acute (<12 weeks after RT) or late

(>12 weeks after RT) toxicity. Local failure of a lesion was defined as either reappearance after complete remission or re-growth after initial partial response in the respective follow-up imaging modality. Overall survival (OS) was calculated from first re-irradiation until death or last follow-up, local control from first re-irradiation until last imaging follow-up.

Statistical analysis:

Regarding radiation treatment parameters, descriptive statistics e.g. median, maximum and minimum values were calculated. Overall survival time (OS) and local control were calculated according to the Kaplan-Meier method. For group comparison, log rank test was used. For statistical analysis, SPSS version 25 was used.

Results

A total of 42 patients were treated with thoracic re-irradiation, 8 (19.2%) of which received a total of three thoracic radiotherapy courses and 2 patients (4.8%) four course of thoracic radiotherapy. 62.5% were treated with a locally ablative dose in a primary or oligometastatic setting at first re-irradiation, 25% of patients were treated with palliative intent for symptom relief. 52.4% of first re-irradiation were performed as SBRT, 23.8% as hypofractionated radiotherapy (single dose $\geq$3 Gy) and the remainder as conventionally fractionated radiotherapy. 69% of patients received concurrent systemic therapy at first re-irradiation. The median time between the first and second course of radiotherapy was 14 months (range 2–184 months). Between second and third course and third and fourth the intervals were 13 months (range 4–31

The median PTV prescription dose (EQD2) was 48.8 Gy_{10} (range 12.5–128.4 Gy_{10}) for all RT courses individually or 54.0 Gy_{10} (range 22–128.4 Gy_{10}), 49.2 Gy_{10} (range 12.5–120.8 Gy_{10}) and 39 Gy_{10} (range 39–39 Gy_{10}) for the individual RT courses respectively. Overall 28.6% of patients had a PTV overlap of more than 25%, 16.8% an overlap of more than 50%. In 28.6% of patients there was an overlap of the 50% isodose lines without an actual PTV overlap. Further dose and dose-volume parameters for the PTV of the accumulated EQD2 dose distributions in table 2.

Regarding OAR, the majority of patients received cumulative doses between 70 Gy_3 and 100 Gy_3 (Table 3). In patients where cumulative OAR doses exceeded 100 Gy_3 the bronchial tree received a maximum D0.1 cc of 187.3 Gy_3 (n = 7, median 130.6 Gy_3), the esophagus a D0.1 cc of 103.8 Gy_3 (n = 1), the aorta a D0.1 cc of 216.1 Gy_3 (n = 5; median 110.2 Gy_3), the Aae. pulmonalis a D0.1 cc of of 187.8 Gy (n = 7, median 121.7 Gy_3). In 19 patients, the cumulative D1cc for the lungs exceed 100 Gy and maxima ranged from 157.9 to 253.9 Gy_3). EQD2 dose statistics for the organs at risk are shown in Table 3.

Regarding clinical outcome the median follow-up from first re-RT was 13 months (range 1–45 months). Median OS of all patients after first re-irradiation was 19 months (range 1–45 months). At the time of analysis 18 patients were still alive. The 12-month local control after a course of re-irradiation was 52.6%. Figs. 1 and 2 show the Kaplan-Meier curves for overall survival and local control measured after the first course of re-irradiation.

In total 80% of patients suffered from a mild G1–G2 toxicity, mostly cough (15%) and dysphagia due to esophagitis (15%). Only one patient suffered from a high grade complication (G5). This patient developed a fatal esophageal rupture 16 months after re-re-irradiation of an NSCLC (esophagus accumulated D1cc = 48.4 Gy_3). Five years prior to reirradiation, this patient was treated with an initial course of radiotherapy with 20 $\times$ 2 Gy to the centrally located tumor and then a second course of SBRT for a lung metastases (dose overlap 8 Gy). Clinically, the patient suffered from a viral esophagitis (Herpes Simplex Virus, HSV) at the time of the rupture. Table 4 shows the acute (<12 weeks) and late (>12 weeks) toxicities after radiotherapy.

When analyzing the outcome of patients with an interval between the courses of radiation treatment of $\leq$6 months and >6 months separately, the median survival of patients with an interval of $\leq$6 months was 14 months (range 1–24 months) and for patients with an interval >6 months 22 months (range 1–45 months). The difference in survival was statistically significant (p = 0.034). Fig. 3 shows the survival in the 2 subgroups.

Table 2
Accumulated EQD2 dose characteristics for the planning target volume (PTV).

	Median	Range
Volume in cc	276	40–1115
V60 Gy_{10} in %	64.10	0–100
V80 Gy_{10} in %	11.00	0–98.5
V100 Gy_{10} in %	4.12	0–88
D1cc in Gy_{10}	108.40	60.7–324.9
Dmax in Gy_{10}	114.10	62.7–363.6
Dmean in Gy_{10}	65.60	35.3–179.6

Discussion

There is no generally accepted recommendation regarding dose, fractionation and volume in case of thoracic re-irradiation, although it is quite commonly performed in recent years with acceptable toxicities and a benefit regarding local or symptom control [4,8,11–15,17,23–31]. Dose schemes depend on a number of factors: total dose in the first RT series, indication of the re-irradiation (symptom control vs. locally ablative treatment), location and distance to organs at risk as well as technical approaches of the treating institution.

The goal of this analysis was to further elaborate on the safety and efficacy of thoracic reirradiation by overlaying all treatment plans with non-rigid image registration after EQD2Gy recalculation, recording cumulative doses to OARs and possibly correlating these with the observed $\geq$ G3 toxicity. There are only few published data based on EQD2 sum plans in patients receiving re-irradiation [9,32].

When looking at the applied EQD2 doses in the sum plans in our analysis, the majority of OAR received cumulative EQD2Gy doses between 70 and 100 Gy_3. Still, for up to 16% of the patients maximum doses (D0.1 cc) to individual organs at risk exceeded doses well above 100 Gy_3, e.g. Aorta (D0.1 cc = 216.11 Gy_3). Yet we report only one high-grade toxicity, which was probably the result of a clinical apparent HSV-esophagitis, although an association with the radiation treatment can't be excluded.

As for the lung as a major organ at risk the median EQD2 Dmean (10.1 Gy; range: 1.9–17.9 Gy_3) and V20Gy_3 (13.6%, range: 3.4–36.7%) in the sum plans were well within dose constraints accepted in the primary treatment setting [20,33–35]. No increased risk for pneumonitis was observed in our cohort. In case of re-irradiation a similar $V_{20\ Gy}$ with 15% and 17% was published by Meijneke et al. and Sumita et al. [9,26]. This probably reflects a strict adherence to common dose constraints for the lung tissue. Sill, high cumulative have also been observed in small volumes in our series without increasing the risk for toxicity (range D1cc up to 253.9 Gy_3). Generally acceptable >G3 lung tissue toxicity has been reported in the literature, emphasizing the feasibility of re-irradiation, especially in smaller volumes [6,8,26,28,32].

A considerable number of patients received a D0.1 cc >70 Gy_3 (n = 24) and >100 Gy_3 (n = 7 to the bronchial tree. There were no incidences of bronchial necrosis, obstruction or bleeding observed.

Table 3
Accumulated EQD2 dose statistics for the organs at risk.

			Median	Maximum	Minimum
Aorta	0.1 cc >70 Gy (n = 19)	D(0,1 cc) in Gy_3	79.10	216.11	70.87
		D(mean) in Gy_3	27.69	44.20	11.01
	0.1 cc >100 Gy (n = 5)	D(0,1 cc) in Gy_3	110.19	216.11	104.43
		D(mean) in Gy_3	35.69	41.41	11.01
Aae. pulmonalis	0.1 cc >70 Gy (n = 23)	D(0,1 cc) in Gy_3	87.24	187.80	70.73
		D(mean) in Gy_3	30.10	64.95	10.83
	0.1 cc >100 Gy (n = 7)	D(0,1 cc) in Gy_3	121.68	187.80	100.39
		D(mean) in Gy_3	23.53	64.95	12.76
Bronchial tree	0.1 cc >70 Gy (n = 24)	D(0,1 cc) in Gy_3	81.99	187.33	70.49
		D(mean) in Gy_3	46.31	63.97	23.19
	0.1 cc >100 Gy (n = 7)	D(0,1 cc) in Gy_3	130.58	187.33	112.32
		D(mean) in Gy_3	31.96	59.06	23.19
Esophagus	0.1 cc >70 Gy (n = 17)	D(0,1 cc) in Gy_3	81.04	103.78	70.15
		D(mean) in Gy_3	32.78	60.57	12.64
	0.1 cc >100 Gy (n = 1)	D(0,1 cc) in Gy_3	103.78	103.78	103.78
		D(mean) in Gy_3	46.08	46.08	46.08
Heart	0.1 cc >70 Gy (n = 4)	D(0,1 cc) in Gy_3	74.61	81.08	70.50
		D(mean) in Gy_3	12.68	18.78	5.61
Lung	1 cc >70 Gy (n = 30)	D(1 cc) in Gy_3	123.88	253.86	72.14
		D(mean) in Gy_3	11.05	17.85	3.25
		V(20 Gy_3) in %	14.86	36.73	2.71
	1 cc >70 Gy (n = 19)	D(1 cc) in Gy_3	157.86	253.86	100.46
		D(mean) in Gy_3	11.02	17.85	3.44
		V(20 Gy_3) in %	14.83	36.73	3.79
Spinal cord	0.1 cc >50 Gy (n = 6)	D(0,1 cc) in Gy_3	57.75	68.30	53.58
		D(mean) in Gy_3	21.38	24.64	18.64

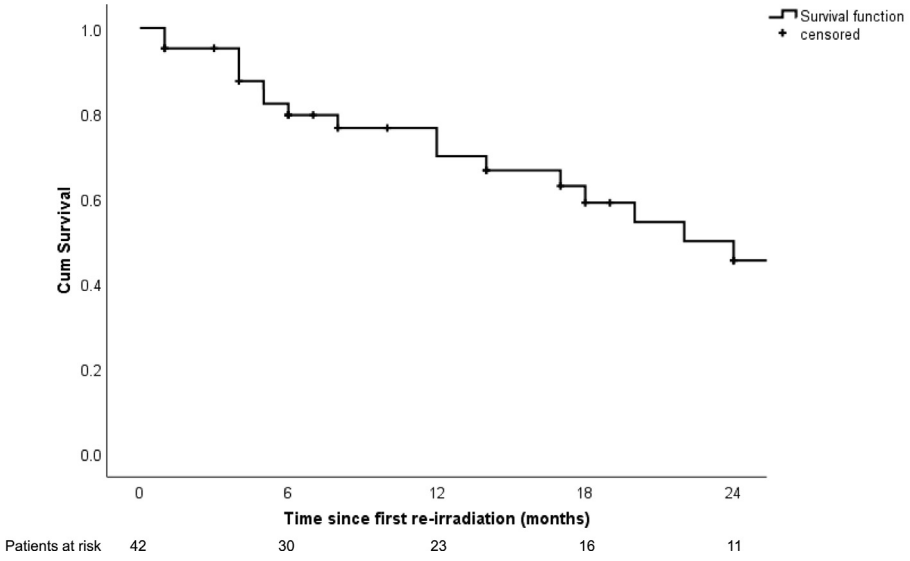

Fig. 1. Survival of patients after first re-irradiation (n = 42).

This is consistent with data published by Brinkley et al. and Ogawa et al. [6,31]. They both reported EQD2 sum doses of >200 Gy_3 to the bronchial tree without ≥G3 toxicity, noticeably with only few patients receiving >100 Gy_3. However, as Peulen et al. pointed out a certain caution should be applied in centrally located tumors with larger target volumes, as they experienced 3 patients with G5 bleeding complications after re-irradiation for centrally located tumors [24]. Total cumulative doses of up to 100 Gy_3 to the bronchial system appear to be safely applicable in the re-treatment setting. Above 100 Gy_3 the data is limited, and toxicities have been observed, although no conclusion can be drawn with regards to safe EQD2Gy doses. Caution should be applied in large, centrally located tumors where retreatment volumes significantly overlap the bronchial tree.

Generally high doses are given to the esophagus also in the primary setting, e.g. for curatively treated lung cancer [21]. Total doses to the esophagus during re-irradiation are usually not much higher, with most patients receiving around 70 Gy_3, only few more than 100 Gy_3 [6,9,26,32]. In our cohort only one patient had a Dmax exceeding 100 Gy_3. Therefore, no firm conclusion can be drawn above 100 Gy EQD2Gy.

Regarding the great vessels, a number of patients received a D0.1 cc of >70 Gy_3 (aorta: n = 19; Aa. pulm.: n = 23), but only few patients (aorta: n = 5; Aa. pulm.: n = 7) D0.1 cc >100 Gy_3. No

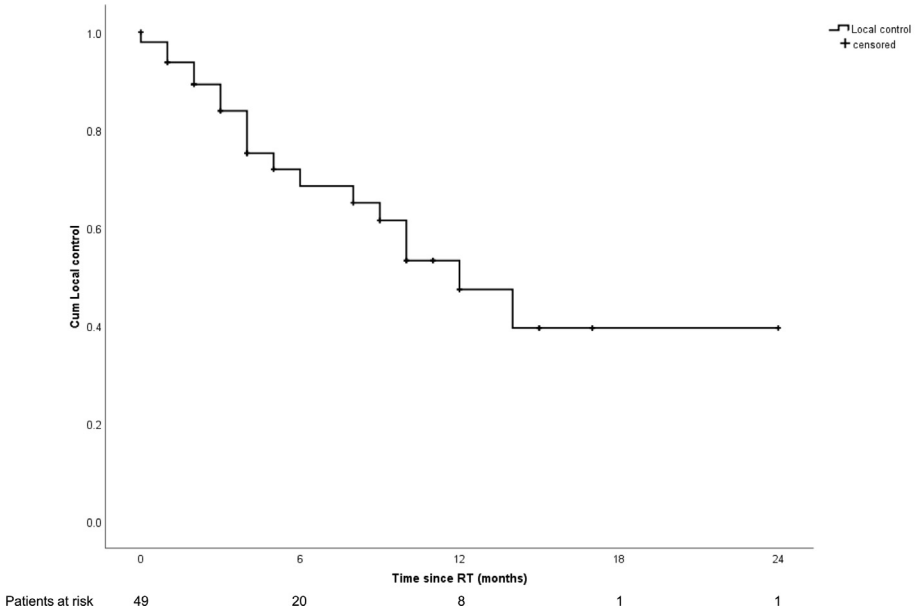

Fig. 2. Local control of lesions after re-irradiation (n = 48).

Table 4
Acute toxicity (<12 weeks) and late toxicity (>12 weeks) after radiotherapy.

	Acute toxicity (<12 weeks)			Late toxicity (>12 weeks)		
	G1–G2	G3–G4	G5	G1–G2	G3–G4	G5
Cough	8	0	0	3	0	0
Dyspnoea	4	0	0	2	0	0
Pneumonitis	1	0	0	1	0	0
Bleeding	0	0	0	0	0	0
Esophagitis	2	0	0	–	–	–
Dysphagia	5	0	0	0	0	0
Pain (Thorax)	1	0	0	0	0	0
Fibrosis	–	–	–	1	0	0
Other	4	0	0	0	0	1*
Sum	30	0	0	8	0	1

* *Esophageal rupture.*

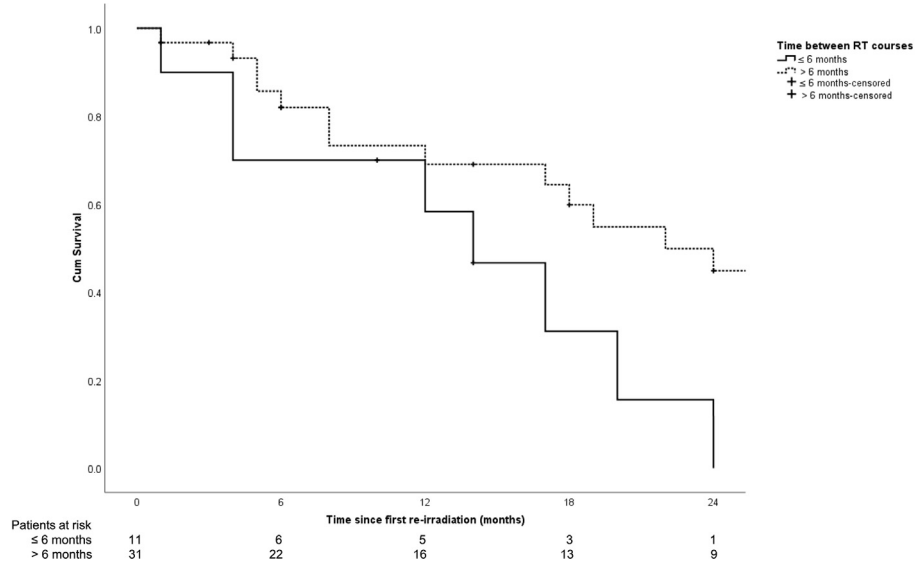

Fig. 3. Survival of patients after first re-irradiation for patients with an interval between RT courses ≤6 months and >6 months (n = 42).

vascular complications were observed. Generally, this is congruent with published data. Binkley et al. published a dose to the aorta of up to 200 Gy_3 without toxicity [32]. Evans et al. however experienced 2 G5 toxicities to the Aorta in 35 patients receiving re-irradiation with a physical dose sum of >120 Gy [36]. Kilburn et al. reported one Grade 5 aorta-esophageal fistula with an estimated EQD2 to the Aorta of 200 Gy [8]. As a conclusion, a total dose of $\leq$100 Gy_3 seems safe in the setting of re-irradiation. Above this, due to the limited number of patients treated there is some uncertainty and severe toxicity has been reported in a small number of patients receiving EQD2Gy doses greater than 120 Gy_3.

The efficacy of the re-irradiation in our cohort was judged by analyzing overall survival (OS) and local control (LC) within the irradiated area. With a median OS of 19 months from the time of first re-irradiation, OS in our cohort was favorable and exceeded most published data for patients with primary lung cancer or lung lesions of different primary entity treated with conventional re-RT with a range of 3–7 months [11–15,25,37,38]. Considerably longer median OS was published by Wu et al. (median survival 14 months) and Griffioen et al. (median survival 13.5 Gy), both including patients with NSCLC and SCLC. They used high dose re-irradiation with a median total dose of 51 Gy (Wu et al.) and 60 Gy (Griffioen et al). Data regarding survival after SBRT, also including patients with primary or secondary lung lesions showed even a better median survival of 20–30 months [6,8,10,17,18,39], with our median OS of 19 months being at the lower published range. In this context we observed that patients with an interval of >6 months between radiation courses had a significantly longer overall survival. Although a selection bias can't be excluded due to the retrospective nature of this data, it also reflects on the dynamic of a disease. For fast progressing disease, the benefit for re-irradiation regarding OS might be limited. This should be taken into consideration for overall treatment decision making.

Regarding local control the 1-year local control of 52.6% in our cohort is within the published range of 52–95%, though at the lower range [9,10,18,24,26,28,40–42]. Given that published data on the higher range of local al control refer to stereotactic re-irradiation, 52.6% is a reasonable local control given that our cohort included both patients re-irradiated in local curative intent with SBRT and a palliative approach. Still, this also reflects the necessity for future research to better define patient cohorts which may benefit most from a re-irradiation approach and then select the appropriate and maximally safe/selective radiation dose according to the treat intent.

Although we observed a wide range of applied doses in our patient cohort, dose–response modelling was not possible due to the low observed rate of late toxicities. Within our reported EQD2 dose ranges re-irradiation, even multiple times appeared to be safe and effective. The strength of our analysis in contrast to previous analysis is that we not only calculated cumulative EQD2 sum plan to investigate maximally applied doses, but also report on dose-volume parameters like D0.1 cc, D1cc, V70–100 Gy to give some guidance of how to interpret and possibly apply our results in daily routine to assure safe re-irradiation. Nevertheless, we are aware that our data suffers the same limitations of virtually all re-irradiation reports due to its retrospective nature and highly selected patient cohorts. There is a need for collection and evaluation of re-irradiation in a prospective manner to get higher quality data with regards to safety, toxicity and quality of life to derive better recommendation for patient selection and safe re-irradiation doses.

Additionally, future research on re-irradiation should explore strategies to improve the therapeutic ratio. Protons for example might offer dosimetrical and biological advantages due to their unique physical properties. Also, new technologies improving on the image guidance and facilitating daily adaptive treatment like the current MR linac implementations might help to reduce the margins necessary to achieve reasonable local control and to reduce OAR exposure to radiation. Systemic treatment option like targeted therapies as well as immunotherapy approaches need to be taken into account as well, either as alternatives to re-irradiation or as companion treatment to allow lower and thus safer radiation dose for an equivalent local effect.

As a conclusion it can be stated that even though several organs at risk received a maximum D1cc of >100 Gy, thoracic irradiation proved to be safe with acceptable toxicities and effective with a good overall survival and local control given the inhomogeneous, "every day" patient population. Nevertheless, prospective data collection with proper analysis of cumulative plan sum are needed to derive robust recommendation for re-irradiation in the thorax.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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